

Adverse events following immunisation – fact and fiction

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Abstract

Immunisation is an extremely safe public health intervention that provides huge health benefits by decreasing morbidity and mortality from infectious diseases. However, because of its success the general public do not experience any of these diseases first hand and so it becomes increasingly difficult to convey the importance of continued immunisation. More recently attention has also focussed on adverse events following immunisation – real or perceived. Post-immunisation surveillance plays a key role in detecting possible adverse events but interpretation of these temporal associations may be complex and can be misleading. This can be problematic when trying to achieve optimal vaccine uptake rates as it becomes difficult for parents to differentiate between fact and fiction. Knowledge of vaccines, their mechanism of action and their potential adverse effects is crucial in providing clear advice to parents. This review will explore some of the more high profile adverse events following immunisation, such as neurological disorders and autoimmune disorders and also focus on vaccine safety in premature infants.

Keywords adverse events; immunisation; infectious diseases; preterm infant; vaccine safety

Introduction

The development of vaccines is one of the greatest medical achievements in the last century. The introduction of vaccines into healthcare has been so successful that we are on the verge of seeing the eradication of many vaccine-preventable diseases. However, because of this success the general public do not experience any of these diseases first hand and so it becomes increasingly difficult to convey the importance of continued immunisation programmes. In addition to this, claims of vaccines causing diseases in the medical literature and particularly in the media, many of which are unfounded, can result in the loss of confidence in vaccines among the general public.

In the past, there have been many allegations concerning vaccine safety, which are not supported by scientific evidence, either at the time or following subsequent focussed research. An obvious

example is the link made between the measles-mumps-rubella (MMR) vaccine, autism and inflammatory bowel disease. In contrast, other adverse events following immunisation are biologically plausible and well documented, such as vaccine-associated paralytic poliomyelitis following the live attenuated oral polio vaccine. Efficient post-licensure surveillance is often essential in quantifying such associations. This was demonstrated by the withdrawal of the Rhesus reassortant rotavirus vaccine following reports of post-vaccine intussusceptions detected through the vaccine surveillance system in the United States.

An important concept in this area is exemplified by the use of the term 'adverse events following immunisation'. This term recognises that the onset of the event was after an immunisation. However, the occurrence of such an event after an immunisation does not imply by itself that the event was caused by the immunisation. In addition, standardisation of the description and definition of the event and the methods by which such events are collected has been variable in the past. This is being addressed through the work of an international collaboration and readers are invited to visit this website for more information (www.brightoncollaboration.org).

This review will explore some of the more high profile adverse events that have been attributed to several routine vaccines. A section on the use of vaccines in preterm infants will highlight recent data on adverse effects in this specific group and emphasise the difficulty in attributing causality when the background rate of adverse events is already frequent.

Pertussis vaccine and neurologic disorders

Before the introduction of the whole cell pertussis vaccine pertussis was a highly prevalent disease causing significant mortality in young children. An alleged association between pertussis immunisation and neurological disorders (encephalopathy and permanent brain damage) was first sparked in Sweden in the 1960s. This was followed by a report in the UK by Kulenkampff in 1974 describing 36 children believed to have developed neurological disorders following the pertussis component of the diphtheria-tetanus-pertussis (DTP) vaccine.¹ Vaccination rates fell from about 81% to 31% resulting in large epidemics as well as deaths from pertussis. Following this, the National Childhood Encephalopathy Study was established. This large study estimated that the risk of permanent brain damage for previously normal children following pertussis vaccine was 1 in 310,000 injections (95% confidence intervals: 1:54,000–1:5,310,000). This estimate included all vaccine-associated cases (onset within 7 days of vaccination) without excluding any with a possible alternative explanation. This is notable as the report reveals that of the 11 cases, an enterovirus was isolated from cerebrospinal fluid in one, another had an 'overwhelming viral infection', another had Reyes syndrome and three others had infantile spasms, a condition for which other aetiologies are likely.² More recent UK and US studies have not identified an increased risk of encephalopathy after whole cell pertussis containing vaccines in infancy.

Interestingly, many children who had been labelled with an encephalopathy following vaccination appear to follow a neurological course similar to that of a condition called severe myoclonic epilepsy in infancy. The gene SCN1A has been recently

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implicated in this condition. One study showed that 11 out of 14 subjects with 'encephalopathy after immunisation' in fact had the SCN1A mutation suggesting that their condition may have been coincidental or triggered rather than caused by immunisation – a possible mechanism for other cases of vaccine associated encephalopathy.³

MMR vaccine and thrombocytopenia

The MMR vaccine is now routinely given in over 100 countries, including those in the European Union, North America and Australasia. Thrombocytopenia has been reported in about 1 per 30,000 to 1 per 1,000,000 MMR doses, occurring within 6 weeks of vaccination. The thrombocytopenia is initially profound but appears to have a benign and short-lasting course with remission being achieved within a few weeks. The occurrence of thrombocytopenia after natural infection with measles and rubella is much higher – approximately 1 in 6000 following measles and 1 in 3000 with rubella. It is rare following wild mumps infection.⁴

A recent study has addressed the issue of the safety of a second MMR dose in children with a previous diagnosis of idiopathic thrombocytopenic purpura (ITP). This found no evidence of an increased risk of ITP after a second dose of MMR vaccine in this group.⁵ Checking the platelet count after immunisation with MMR vaccine in patients with a history of ITP may, therefore, not be necessary.

Hepatitis B and multiple sclerosis

The association between the hepatitis B vaccine and multiple sclerosis (MS) was first suggested in 1996 when several cases of MS or demyelinating disease were described after vaccination with hepatitis B vaccine in France. This resulted in widespread public concern in that country. In response to the decreased acceptance of hepatitis B vaccine, the World Health Organisation set up an expert panel to examine the available evidence. While admitting that the available data were scant, they concluded that there was not enough evidence to suggest an association and recommended the continued use of the vaccine.

There have been a few epidemiological studies suggesting a causal relationship between hepatitis B vaccine and MS and others that have concluded the opposite. Re-analysis of these studies has concluded there is not enough evidence to establish the existence of an increased risk of MS associated with hepatitis B vaccine in adults.⁶

A recent case-control study assessed the risk of a first episode of MS in childhood after hepatitis B vaccine and found there to be no increase.⁷ In addition, incidence rates of MS in a study in British Columbia showed no difference before and after the introduction of the hepatitis B vaccine immunisation programme at 11–12 years of age.

Considering possible mechanisms, studies looking at the T-cell responses to hepatitis B surface antigen in subjects vaccinated with hepatitis B vaccine could not find any differences between healthy subjects and those with MS. Furthermore, studies looking at human leukocyte antigen haplotypes between immunised and non-immunised MS subjects also demonstrated no differences.

Influenza vaccine and Guillain-Barré syndrome

Influenza is an acute viral infection of the respiratory tract and is highly infectious. Neonates, the elderly, those with underlying disease or those who are immunocompromised are at higher risk of serious illness and mortality from influenza. Influenza immunisation programmes aim to protect those vulnerable groups at risk of serious morbidity and mortality from influenza. In the UK, the influenza vaccine is offered to all those aged 65 years or over, all those aged 6 months or over with underlying disease or who are immunosuppressed, and those who work in the healthcare profession.

In 1976, after the introduction of the influenza 'swine-flu' vaccine, there were reports of an increased frequency of Guillain-Barré syndrome. Recipients of the vaccine had a relative risk of 7.6 for developing Guillain-Barré syndrome.⁸ Other influenza vaccines were then used, but another study that focussed on the 1992–1994 vaccine campaigns in the US demonstrated a very small but statistically significant increased risk of developing Guillain-Barré syndrome. This increased risk was of the order of about one additional case of Guillain-Barré syndrome per million persons vaccinated against influenza. This study also suggested that influenza vaccines other than the swine-flu vaccine might be responsible for an increased risk of Guillain-Barré syndrome.⁹ In contrast, a recent study of cases of Guillain-Barré syndrome in the UK could not show an increased risk following any vaccine.¹⁰ Further studies need to be undertaken to assess the risk of relapse after vaccination for those individuals who already have MS.

Influenza vaccine and oculo-respiratory syndrome

Oculo-respiratory syndrome is a combination of ocular (red eyes) and respiratory symptoms (respiratory distress, throat tightness or chest discomfort) with facial oedema with or without systemic symptoms, such as fever. It was first reported as an adverse event following immunisation with the influenza vaccine in Canada in 2000. First-time recipients and atopic subjects appeared to be more susceptible. Recurrence of oculo-respiratory syndrome after revaccination was low and it was usually milder than the first episode. Oculo-respiratory syndrome was associated with a single influenza vaccine found to have large aggregates of unsplit viral particles. Changes were subsequently made to the manufacturing process of the influenza vaccine. Since the introduction of this vaccine there has been a reduction in the number of reports of oculo-respiratory syndrome.

Interestingly, a prospective study in a large group of immunised infants and toddlers and their household contacts found oculo-respiratory symptoms to be infrequent with no difference in frequency between immunised and non-immunised household members.¹¹

Symptoms of oculo-respiratory syndrome resemble allergy and it may be mislabelled as an allergic reaction to the influenza vaccine. Skin tests show that this syndrome is not a type 1 immunoglobulin (IgE)-mediated hypersensitivity reaction. Because of the similarities, healthcare providers may tend to withhold further influenza vaccine doses. Current recommendation for subjects who have had oculo-respiratory syndrome following the influenza vaccine is to revaccinate if ongoing protection is required.

Therefore, differentiating between oculo-respiratory syndrome and an allergic reaction is essential as severe allergy is a contraindication to further doses. One suggestion is that skin testing of those patients who have had oculo-respiratory syndrome be carried out prior to revaccination.

Nasal influenza vaccine and Bell's palsy

Bell's palsy was reported as an adverse event following immunisation with a Swiss inactive nasal formulation of the influenza vaccine, introduced in 2000. This vaccine is prepared with an *Escherichia coli* heat-labile toxin (a mucosal adjuvant). Possible causes for the increase in Bell's palsy after intranasal administration of the Swiss influenza vaccine include the triggering of Herpes simplex virus reactivation by the adjuvant, neurotoxicity of enterotoxins in the adjuvant, and a vaccine-directed autoimmune response. This Swiss influenza vaccine has since been withdrawn, and another intranasal influenza vaccine (trivalent, live, attenuated) that does not contain an adjuvant has been used widely since 2003. This vaccine has not been associated with an increased risk of Bell's palsy. There have also been concerns of a possible increased risk of Bell's palsy with parenteral influenza vaccine based on passive reports through the US Vaccine Adverse Event Reporting System. However, a large population-based study using the UK General Practice Research Database showed no increased risk of Bells' palsy following parenteral influenza or pneumococcal vaccines.¹²

Haemophilus influenzae type b vaccine and diabetes

Haemophilus influenzae can cause serious invasive disease. *H. influenzae* type b (Hib) most commonly presents as meningitis, epiglottitis and bacteraemia and can also cause septic arthritis, osteomyelitis, cellulitis, pneumonia and pericarditis. The introduction of the Hib conjugate vaccine has been a major success in reducing the numbers of invasive Hib disease.

Concerns have been raised in the past about a possible association between Hib vaccine and type 1 diabetes. One group used data from diabetes registries in Sweden and Finland to compare changes in the incidence of type 1 diabetes with changes in the national immunisation schedules. Their analysis showed an increase in the incidence of type 1 diabetes after the introduction of the Hib vaccine in 1988.¹³ The mechanism proposed was autoimmune with the development of pancreatic autoantibodies leading to pancreatic damage. They were not, however, able to determine whether children who were vaccinated had a higher rate of diabetes than unvaccinated children during the same time period. In contrast to this study, other controlled studies have found no increased risk of diabetes with introduction of the Hib vaccine. Furthermore, a large study of Danish children did not show a causal relation between any childhood vaccination and type 1 diabetes.¹⁴

DTP vaccine and sudden infant death syndrome

A link between vaccines and sudden infant death syndrome (SIDS) has been suggested in the past largely due to the temporal association between the first immunisations, in particular DTP vaccines, and the peak incidence of SIDS. However, other studies

have suggested that this event occurs no more frequently following vaccination than it does by chance. A large case control study conducted in Germany for example, collected immunisation data on 307 SIDS cases and 971 controls and found no increased risk of SIDS in the 14 days following immunisation.¹⁵ This study, like others, demonstrated that immunisation was in fact, protective against SIDS. One possible explanation is that immunisation provides protection against unrecognised pertussis – a potential cause of sudden and unexpected death in this age group.

In addition, 'Back to Sleep' campaigns have resulted in a significant fall in the number of reports of SIDS. This adds to the notion that the temporal association between immunisation and SIDS is not causal.

Rubella vaccine and arthralgia/arthritis

Adverse events following immunisation with rubella vaccine involving joints are well recognised. These include transient arthralgia, acute arthritis and chronic arthritis, albeit rarely. The arthritis usually resolves with no residual effects. Arthritis is a common complication of wild rubella virus in adults, but it occurs less often in children. Arthritis as an adverse event following immunisation has been described following the administration of the MMR vaccine in children. In a study looking at joint and limb symptoms in children 6 weeks after immunisation with MMR vaccine, an increased risk of joint symptoms (arthralgia or arthritis) was described. It is clear that the risk of arthritis following immunisation is far lower than after wild rubella infection.¹⁶

Pertussis and extensive limb swelling

The replacement of the diphtheria-tetanus-whole cell pertussis (DTwP) vaccine with the acellular pertussis based combination (DTaP) has resulted in fewer and less severe local and systemic reactions. However, episodes of extensive limb swelling (swelling at the injection site extending to the adjacent joints) have been reported in about 2% of children, particularly after receiving fourth and fifth doses of DTaP.¹⁷ The swelling generally resolves in about 4 days, leaving no residual sequelae. Extensive limb swelling has been described with all licensed DTaP vaccines. One hypothesis is that this represents an Arthus reaction due to the presence of high levels of pre-vaccination antibodies, which is responsible for the extensive limb swelling.

In a slightly different setting, the importance of deep intramuscular administration in minimising local reactions, such as swelling has been demonstrated. In this study the use of longer needles was shown to reduce local reactions following vaccination with DTwP, Hib and a serogroup C meningococcal conjugate vaccine, presumably by ensuring intramuscular rather than subcutaneous deposition of vaccine.¹⁸ However, it is unlikely that this mechanism would explain the extensive limb swelling reactions associated with DTaP.

Vaccine components

Vaccines contain components other than the vaccine antigens themselves. These include adjuvants and preservatives. Aluminium salts are utilised as adjuvants in vaccines and thiomersal, a mercury derivative, is used as a preservative. Evidence for any

adverse effects directly caused by these components is scarce and parents should be reassured that these components are likely to be harmless. Thiomersal has in fact been removed from most vaccines now as its preservative action is no longer required in the era of single vial vaccines.

Immunisation of the preterm infant

A particular group of infants that are at increased risk of infections, including vaccine preventable infections, are those born prematurely. Despite the importance of vaccinating this group on time they are in fact more likely to have delayed vaccination schedules. This may reflect some hesitancy and anxiety among parents and clinicians concerning safety and efficacy. Some of this has been fuelled by reports of apnoeas and cardiorespiratory events following immunisation.

Immunisation guidelines for preterm infants recommend vaccinating with all routine vaccines at the same postnatal age as term infants (i.e. without correction for gestational age). Immunogenicity studies support this concept as protective concentrations of antibodies are generally achieved. A number of studies have reported adverse events following immunisation, with a particular focus on those infants who are still in hospital at the time of their vaccination, and report cardiorespiratory events in up to 49% of vaccinees. One important study revealed that it was those infants with cardiorespiratory symptoms before immunisation that were most likely to have them after immunisation. This study also noted that there were no overall deleterious consequences on their clinical course.¹⁹ In another study, infants with pre-immunisation apnoea had a 25-fold increased risk for apnoea within 48 hours of immunisation. Moreover, those infants with more than one apnoeic episode before immunisation were likely to have apnoeic episodes post-immunisation. For preterm infants with no apnoeic episodes prior to immunisation predictors for post-immunisation apnoea included increased illness scores at birth, younger age at immunisation and weight less than 2000 g.²⁰ These studies remind us that 'adverse events' such as these occur commonly in preterm infants, in the presence or absence of vaccination. Preterm infants who are still in hospital at 2 months of age should be vaccinated on time but it makes sense to avoid vaccination until they are free of severe cardiorespiratory events and then to monitor all of them for up to 48 hours afterwards.

Conclusion

We are indeed in a fortunate position to be able to contain important infectious diseases, especially childhood infectious diseases, through vaccination. Vaccines are generally safe and provide huge health benefits by decreasing morbidity and mortality from infectious diseases. However, it is to be expected that with fewer cases and less morbidity and mortality from vaccine preventable disease seen by the public, attention will be drawn to rare adverse events, whether real or alleged. Most alleged adverse events stem from misleading temporal associations. As the majority of infants are vaccinated with an immunisation schedule beginning early in the first year of life and extending into the second year, the likelihood of any event occurring by chance around the time of the administration of a vaccine is great. Of course, a number of events that follow immunisation are indeed related to the vaccine

or the vaccination process. These are often biologically plausible and have been well studied. It is vital that practitioners acknowledge this and are aware of these events so that they can offer the correct information and guidance regarding immunisation.

Although at times it may be difficult to deal with alleged adverse events, it is important that any such events are taken seriously and addressed through appropriate research. This may include pre-licensure safety assessments but often will require continued or enhanced post-licensure surveillance, including case control studies. Continued basic research concentrating on vaccine constituents and the mechanisms leading to adverse reactions are also important. Appropriate attention to adverse events following immunisation is also a critical step towards the eradication of vaccine-preventable diseases.

"An ounce of prevention is worth a pound of cure"

Conflict of interest

Both authors have received funding from vaccine manufacturers as well as other sources to conduct research. ◆

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